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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,137	08/17/2005	Rian Van Meeteren	Q84960	6831
23373	7590	09/22/2006	EXAMINER	
SUGHRUE MION, PLLC 2100 PENNSYLVANIA AVENUE, N.W. SUITE 800 WASHINGTON, DC 20037			ROYDS, LESLIE A	
			ART UNIT	PAPER NUMBER
			1614	

DATE MAILED: 09/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/517,137

Applicant(s)

VAN MEETEREN ET AL.

Examiner

Leslie A. Royds

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 June 2006 and 18 July 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 7-11 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 7-11 is/are rejected.
- 7) ☒ Claim(s) 11 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>23 May 2006</u> . | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Claims 7-11 are presented for examination.

Applicant's Amendment filed June 19, 2006 and Supplemental Amendment filed July 18, 2006 have each been received and entered into the present application. Accordingly, the specification at paragraph 28, pages 11-12 has been amended. Applicant's Information Disclosure Statement (IDS) filed May 23, 2006 has also been received and entered into the application. As reflected by the attached, completed copy of form PTO/SB/08A (one page total), the Examiner has considered the cited references with the exception of the reference to Ning, which was not provided in Applicant's submission and could not be located after a reasonable search by the Examiner.

Claims 7-11 are pending and are under examination. Claims 1-6 have been cancelled, claims 7-8 are amended, and claims 9-11 are newly added.

Applicant's arguments, filed June 19, 2006, have been fully considered but they are not deemed to be persuasive. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Objection to the Claims (New Ground of Rejection)

Claim 11 is objected to for failing to capitalize the word "the" at the beginning of the claim.

Claim Rejections - 35 USC § 112, First Paragraph, Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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Claims 7-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of overactive bladder occurring in the presence of a pathological factor (e.g., bladder outlet obstruction or the like), does not reasonably provide enablement for the treatment of overactive bladder appearing in the absence of a pathological, neurological or metabolic factor that would account for the presence of such a condition, for the reasons already of record at pages 3-8 of the previous Office Action dated December 19, 2005, of which said reasons are herein incorporated by reference.

Newly added claims 9-11 are properly included in the present rejection because each is dependent upon independent claims 7 or 8, which lack enablement for the treatment of overactive bladder appearing in the absence of a pathological, neurological or metabolic factor for the reasons previously made of record at pages 3-8 of the Office Action dated December 29, 2005. Insofar as newly added claims 9-11 fail to remedy the lack of enablement of this aspect of using the invention commensurate in scope with the claims, rejection of present claims 9-11 as also lacking enabling direction is proper in this regard.

Applicant's remarks have been fully considered in their entirety, but fail to be persuasive.

In response to the conclusion of a lack of enablement under 35 U.S.C. 112, first paragraph, Applicant states that the animal model used in the disclosed examples is a valid model for the treatment of overactive bladder and that experiments using female rats with partially obstructed urethras were commonly used in the art for evaluation of bladder contraction (i.e., bladder instability, also known as overactive bladder).

First, the conclusion that the present claims lack enablement was not predicated on the fact that the animal model used in the disclosed examples of the specification is not a valid animal model. In fact, the art and Applicant's cited references proves to the contrary, i.e., that such an animal model is frequently used in studies of overactive bladder. However, the issue at hand is that the animal model upon which Applicant relies to provide enabling support to the presently claimed method of treating overactive bladder, wherein overactive bladder is defined as the "medical condition referring to the

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symptoms of frequency and urgency, with or without urge incontinence, *when appearing in the absence of local pathological, neurological or metabolic factors that would account for these symptoms*” (see page 6, paragraph 3 of the present specification), is the treatment of a female mouse model with total bladder outlet obstruction by administering tamsulosin or tamsulosin in combination with solifenacin succinate, which is not the same type of host presently claimed.

Though Applicant provides a working example of treating female patients with tamsulosin for overactive bladder, it is first noted that the Example does not provide criteria or a protocol by which to select those patients that exhibit overactive bladder symptoms in the absence of a pathological, neurological or metabolic factor, i.e., the same host presently claimed, for this experiment. Additionally, this example is procedural in nature, was not reduced to practice and, thus, does not actually arrive at any conclusion of a notable positive therapeutic effect. While the lack of a working embodiment that has actually been reduced to practice cannot be the sole factor in determining enablement, the absence of substantial evidence commensurate in scope with the breadth of the presently claimed subject matter, in light of the unpredictable nature of the art and the limited direction that Applicant has presented, provides additional weight to the present conclusion of insufficient enablement in consideration of the *Wands* factors as a whole.

It is clear that Test Example 1 (procedural example directed to the treatment of female patients with overactive bladder) cannot be relied upon for enabling support of the presently claimed method for the deficiencies described *supra*. However, Test Example 2 cannot be relied upon for enabling direction because the example is directed to the activity of tamsulosin or tamsulosin in combination with solifenacin succinate in overactive bladder resulting from total bladder outlet obstruction, which is not the same host type presently claimed (i.e., overactive bladder in the absence of pathological, neurological or metabolic factors that would account for these symptoms).

As stated *supra*, it is reiterated that the lack of a working embodiment is not the sole factor in

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concluding a lack of enablement, but does provide additional weight to the assertion that the specification lacks an enabling disclosure of the claimed subject matter when considered in light of the complex nature of the art at the time of the invention. Applicant is reminded that a conclusion of a lack of enablement must take into consideration the unpredictability in the art at the time of the invention and the direction or guidance provided by Applicant. The amount of guidance required to be present in the specification as originally filed is directly proportional to the amount of knowledge in the art as well as the unpredictability in the art. In other words, if little or nothing is known in the prior art about an aspect of the claimed invention and the art is unpredictable, the specification needs more detail and guidance as to how to use the invention in order to be enabling. Please reference *In re Fisher*, 417 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) and *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004).

However, Applicant has failed to rebut the unpredictability in the art with regard to the treatment of idiopathic overactive bladder either in the present disclosure or in response to the state of the art as presented by the Examiner in the previous Office Action. Given that the effective treatment of patients with idiopathic overactive bladder is highly unpredictable due to the fact that there is no physiological “mechanism” (i.e., nerve condition via the central or peripheral nervous system, etc.) from which such a condition results that can be targeted for treatment to eliminate symptoms of overactive bladder, and further in light of the vast number of mechanisms that have been attributed, even remotely, to the development of overactive bladder, the skilled artisan would have been skeptical to extrapolate the results shown in treating an overactive bladder mouse model with total bladder outlet obstruction to subjects with overactive bladder *in the absence of a substantive, pathophysiological abnormality*. In short, the specification lacks an enabling disclosure of this aspect of the invention and would require undue experimentation in order to determine how to use the presently claimed tamsulosin or tamsulosin/solifenacin succinate combination for treating idiopathic overactive bladder with a reasonable

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expectation of success.

Though enablement of an invention does not rest solely on the disclosure of a working example, as noted in the MPEP at §2164.02, "The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it *without* an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)" (emphasis added). It is clear that the specification lacks sufficient direction or guidance as to how to practice the use of tamsulosin or tamsulosin in combination with solifenacin for the treatment of idiopathic overactive bladder without an undue level of experimentation, which is directly contrary to the instruction of 35 U.S.C. 112, first paragraph (i.e., Applicant must describe his invention in "such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same.")

For these reasons, and those previously made of record at pages 3-8 of the previous Office Action dated December 19, 2005, rejection of claims 7-11 remains proper and is **maintained**.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner

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to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 7-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sellers et al. ("Potential Therapeutic Targets for Treatment of the Overactive Bladder", *World Journal of Urology*, 2001) in view of Caroon et al. (U.S. Patent No. 6,319,920; 2001) and Remington's Pharmaceutical Sciences (1980; pages 420-425), each already of record, and further in view of newly cited Takeuchi et al. (EP 0801067, 1997; previously cited by the Examiner), for the reasons of record set forth at pages 14-18 of the previous Office Action dated December 19, 2005, of which said reasons are herein incorporated by reference.

Newly added claims 9-11 are properly included in the present rejection because Sellers et al. teaches the activity of the compound tamsulosin for the treatment of overactive bladder in the absence of significant bladder outlet obstruction. The use of the hydrochloride salt of tamsulosin would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention because Remington's Pharmaceutical Sciences provides teachings that pharmaceuticals may be formulated into salts to modify the duration of action of a drug; to modify the transportation and distribution of the drug in the body; to reduce toxicity; and to overcome difficulties encountered in pharmaceutical formulation procedures or in the dosage form itself (column 2, page 424, first paragraph). In light of such teachings, the use of tamsulosin hydrochloride would have been obvious to the skilled artisan motivated by any one or more of these factors to enhance the pharmacokinetic parameters of the drug or to reduce the toxicity with the reasonable expectation that the therapeutic benefit of the agent in hydrochloride salt form would have been the same or substantially similar to that of the agent itself.

Regarding the use of the 3-quinuclidinyl-1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate as the muscarinic receptor antagonist, the use of such a compound would have been *prima facie* obvious to the skilled artisan because Takeuchi et al. (EP 0801067; 1997) provides teachings that the quinuclidine

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derivative compound 3-quinuclidnyl-1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate was known in the art as having activity as a muscarinic receptor antagonist, which when taken in combination with Caroon et al., who teaches the efficacy of treating overactive bladder using muscarinic receptor antagonists, would have raised the reasonable expectation of success that such a quinuclidine derivative compound would have demonstrated the same, or substantially similar, activity in treating overactive bladder as the other muscarinic receptor antagonists taught by Caroon et al.

Applicant's remarks have been carefully considered in their entirety, but fail to be persuasive.

In response to the rejection set forth over Sellers et al., Applicant states the rejection improperly relies upon hindsight because "only by reference to the data in the present specification can the Examiner state that one of ordinary skill in the art would expect tamsulosin to be useful to treat overactive bladder." (see page 8 of Applicant's remarks) Applicant further submits that Sellers et al. teaches that two specific alpha-1-adrenoreceptor antagonists (tamsulosin and Rec 15.27329) act entirely differently and that Sellers et al. states that "if the alpha-1-adrenoreceptors do play a role in the actions of alpha-1-adrenoreceptor antagonists on lower urinary tract symptoms, the action may be at the level of the central nervous system or spinal cord rather than the bladder itself, thereby suggesting that any potential use would be for the treatment of overactive bladder associated with a pathological cause, which is not the condition treated in the present method claims." (see also page 8 of Applicant's remarks) Finally, Applicant relies upon the results from Test Example 2 to show that tamsulosin and solifenacin in combination exhibit unexpected synergy.

Regarding Applicant's assertion that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and

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does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. Please see *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In the present case, the Examiner's conclusion of obviousness is not based upon hindsight reasoning, but rather is grounded in the unequivocal and unambiguous teachings of the prior art of Sellers et al. The conclusion that the compound tamsulosin would have activity in treating overactive bladder without pathological cause is clearly set forth in the teachings of Sellers et al. See the previous Office Action dated December 19, 2005 at pages 13-14. Sellers et al. expressly teaches the activity of tamsulosin in treating irritative symptoms of urinary frequency, nocturia, urinary urgency, etc. *in patients who do not have significant bladder outlet obstruction*, i.e., no pathological cause. Please see Sellers et al., page 308, column 1, paragraph 3.

It is irrelevant that the two alpha-1-adrenoreceptor antagonists tamsulosin or Rec 15/2739 act entirely differently. The mechanism of action of tamsulosin is inconsequential to the fact that it has clearly and unequivocally demonstrated efficacy in treating the irritative symptoms of overactive bladder in patients with overactive bladder in the absence of outlet obstruction, regardless of the conductive mechanism or nervous center (i.e., central nervous system or spinal cord) by which it exerts such an effect.

Finally, Applicant's assertion of unexpected results cannot be afforded the significance that Applicant has requested because Applicant is attempting to establish unexpected results in an animal model host that is not the same as that claimed. In other words, whatever effect, synergistic or not, that Applicant has observed in the treatment of mice with overactive bladder with total outlet obstruction is clearly not commensurate in scope with what is claimed, i.e., treatment of patients overactive bladder without pathological cause, and is, therefore, not at all persuasive.

For these reasons, and those previously made of record at pages 14-18 of the previous Office Action dated December 19, 2005, rejection of claims 7-11 remains proper and is **maintained**.

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Conclusion

Rejection of claims 7-11 remains proper and is **maintained**.

No claims of the present application are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

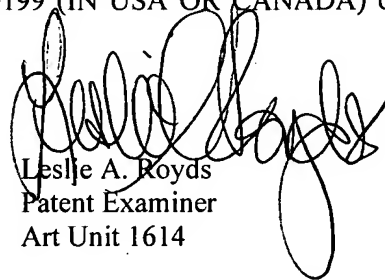
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

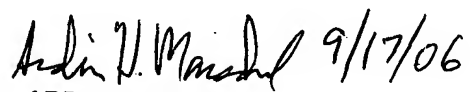
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Leslie A. Royds
Patent Examiner
Art Unit 1614

September 14, 2006



ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER